Netherlands
The Journal of Medicine

REVIEW

Established and forthcoming drugs for the treatment of osteoporosis

W.F. Lems[1]*, M. den Heijer[2]

Departments of [1]Rheumatology and [2]Internal Medicine, VU University Medical Centre, Amsterdam, the Netherlands, *corresponding author: e-mail: wf.lems@vumc.nl

ABSTRACT

Nowadays, effective drugs are available to prevent fractures in patients at high risk for osteoporotic fractures. The generic bisphosphonates alendronate and risedronate are first choice, because of their effectiveness and tolerability in the majority of patients, while they also have a low cost price. However, the use of bisphosphonates can be associated with side effects: not only the well-known (upper) gastrointestinal side effects, but also (spontaneous) atypical fractures of the femur and aseptic necrosis of the jaw.

Denosumab and zoledronic acid are both potent antiresorptive drugs that could be an attractive alternative for those patients who do not tolerate oral bisphosphonates. Strontium ranelate has both antiresorptive and anabolic effects, while teriparatide has primarily anabolic effects. The working mechanism of cathepsin K inhibitors and monoclonal antibodies against sclerostin, both currently under development, is exciting since the usually occurring coupling of bone resorption and bone formation has not been found so far.

KEYWORDS

Osteoporosis, bisphosphonates, denosumab, cathepsin K inhibitor

INTRODUCTION

Osteoporosis is a skeletal disease that is characterised by low bone mineral density (BMD) and a microarchitectural deterioration of bone tissue, leading to decreased bone quality and an elevated risk of fractures.[1] Patients 50 years and over with a recent clinical fracture and a low BMD, and elderly patients with (several) clinical risk factors for osteoporosis, such as low BMI, familial osteoporosis and immobility, and a T-score below -2.5 at the lumbar spine and/or hips are usually prescribed antiosteoporotic treatment.[2] In addition, elderly osteopenic patients (T-score between -1 and -2.5) who are on chronic treatment with prednisone (>7.5 mg per day) or elderly osteopenic patients with one or more vertebral fractures, are also offered antiosteoporotic treatment.[3] General measures are necessary in all osteoporotic patients: adequate calcium and vitamin D intake, regular (weight-bearing) exercises, prevention of falls, smoking cessation and avoiding (a large intake of) alcohol.[2]

In this manuscript we will discuss the effectiveness and side effects of the antiosteoporotic drugs calcium and vitamin D supplements, oral bisphosphonates, strontium ranelate, raloxifen, zoledronic acid, and also new drugs with exciting working mechanisms that either have a stimulating effect on bone formation (teriparatide, PTH 1-84), selectively block RANKl (denosumab), or are currently under development (cathepsin K inhibitors, monoclonal antibodies against sclerostin).

CALCIUM AND VITAMIN D

Vitamin D plays a pivotal role in the uptake of calcium and also has direct effects on bone. Vitamin D and calcium deficiency leads to secondary hyperparathyroidism and osteoporosis and osteomalacia.[4] Therefore, adequate vitamin D and calcium status is the very basis of osteoporosis prevention and treatment. This is illustrated by the fact that almost all trials on antiosteoporotic drugs use vitamin D and calcium supplementation in both the active and the placebo arm. Much debate exists on which levels of 25-hydroxy vitamin D are necessary with regard to the prevention of bone loss. In the Netherlands, the 2008 report of the Health Council advised a level of 50 nmol/l as sufficient.[5] Recently,

the Institute of Medicine declared the skeletal effects of vitamin D as the only proven effect and also recommended a level above 50 nmol/l.[6] Based on these levels patients with osteoporosis are advised to take 800 IE vitamin D daily.[2,5] Patients with coeliac disease and other bowel disorders with intestinal malabsorption should be tested whether they achieve these levels. Furthermore, patients with chronic kidney disease should receive calcitriol or another active vitamin D because of low 1-alpha hydroxylase activity.

The recommended daily allowance (RDA) for calcium in adults is 1000-1200 mg.[6] Some concern was raised after the publication of a meta-analysis that showed an increased risk for cardiovascular disease in subjects treated with higher doses of calcium alone (without vitamin D).[7] However, a number of issues with the studies, such as inadequate compliance with the intervention, use of non-trial calcium supplements, potential bias in event ascertainment, and lack of information on and adjustment for known cardiovascular risk determinants, suggest that bias and confounding cannot be excluded as explanations for the reported associations.[8] Findings from other cohort studies also suggest no detrimental effect of calcium from diet or supplements, with or without vitamin D, on cardiovascular disease risk. So the current RDA of 1000-1200 mg still holds.[2]

BISPHOSPHONATES

Where lifestyle recommendations such as weight-bearing exercises, fall prevention, smoking cessation and the use of sufficient calcium and vitamin D is essential to all osteoporosis prevention, in patients with documented osteoporosis this will not be sufficient. Bisphosphonates have been cornerstone in osteoporosis treatment for a long time. The first trials were done in the 1970s. Bisphosphonates have a structure that resembles hydroxyapatite and are built into the bone. They are toxic for the osteoclasts by interfering with adenosine triphosphate (ATP) in the energy metabolism (non-nitrogenous bisphosphonates) or with the HMG-CoA reductase system (nitrogenous bisphosphonates) and therefore act primarily as antiresorptive agents. More than ten different bisphosphonates are available for both oral and intravenous use.

Etidronate is one of the first bisphosphonates used in clinical practice, but its antiresorptive potency is low compared with more recently developed nitrogenous bisphosphonates (such as alendronate, risedronate, and zoledronic acid). Because etidronate at higher doses can induce mineralisation defects (osteomalacia), the nitrogenous bisphosphonates are now recommended. Because of the data showing a reduction in vertebral and nonvertebral fractures, including hip fractures, the long-term experience, the tolerability in the majority of patients and the low cost price of the generics, alendronate and risedronate are first choice.[2]

Other bisphosphonates, e.g. ibandronate, tiludronate and pamidronate, also reduce bone resorption, but fracture reduction (vertebral, nonvertebral and hip fracture) has not been documented.

The main problem in oral therapy is to achieve the desired levels in the blood. For most patients the oral form will be sufficient, but in cases of gastrointestinal symptoms or gastrointestinal contraindications, the intravenous form could be chosen. Although several intravenous bisphosphonates are available, zoledronic acid has been most extensively studied and showed a strong reduction in both vertebral and nonvertebral fractures.[9]

One of the side effects of oral bisphosphonates is the damage to the oesophageal mucosa which can result in ulcers and eventually in oesophageal cancer. Therefore patients should be told to take these pills in a fasting state and to remain in an upright position for half an hour. Given these recommendations bisphosphonate use turned out not to be associated with a higher incidence of oesophageal cancer.[10]

In the last decade two other side effects became apparent, osteonecrosis of the jaw (ONJ) and atypical fractures.[11] Both are thought to result from the low bone turnover state that is induced by the bisphosphonates. Although the primary effect is antiresorptive, the close connection between osteoclasts and osteoblasts results not only in decreased bone resorption but also decreased bone formation in the long term.

Osteonecrosis of the jaw occurs more often in patients with periodontitis. Therefore doctors prescribing bisphosphonates should ask about dental history and dentists should ask about bisphosphonate use in their patients. It is important to realise that the risk of ONJ is much higher in patients with a malignancy and who are treated with several courses of intravenous bisphosphonates than in postmenopausal osteoporotic women treated with oral bisphosphonates.

Atypical subtrochanteric hip fractures are a relatively recently discovered side effect of long-term bisphosphonate treatment. It is a fracture in the subtrochanteric or shaft region with a transverse or short oblique orientation and with a thickening of the cortex. This type of fracture is most often reported in combination with long-term (>5 years) bisphosphonate use. Although these side effects of bisphosphonates may be serious, the incidence is relatively low. However, especially the occurrence of atypical fractures in long-term bisphosphonate use has warranted a more restricted use and the introduction of a 'drug holiday' of two to three years after the initial treatment for five years.

Most trials with bisphosphonates excluded patients with chronic kidney disease (CDK), especially with an estimated creatinine clearance below 30 ml/min. Next to the paucity of data an important reason to withhold bisphosphonates in CKD patients is the occurrence of other bone diseases that result in a lower bone density (for instance renal osteodystrophy).[12]

STRONTIUM RANELATE

Strontium ranelate is a unique drug, since it has a combined effect with stimulation of bone formation and inhibition of bone resorption. Strontium is an elementary element such as calcium and is named after the Scottish place, Strontian, were this element was found.[13] It has been used for osteoporosis for a long time. Strontium ranelate acts on the surface of the bone and stimulates the differentiation of osteoblasts by stimulating the calcium sensor receptor, but inhibits osteoclast differentiation by inhibiting RANKL production and increasing osteoprotegerin (OPG) activity.

Two phase III trials show a clear effect on the prevention of vertebral fractures: the Spinal Osteoporosis Therapeutic Intervention study (SOTI) with 1649 postmenopausal women with osteoporosis and at least one vertebral fracture showed a 41% reduction in new vertebral fractures after three years.[14] The TReatment Of Peripheral OSteoporosis study (TROPOS) with 5091 postmenopausal women with osteoporosis also showed, in three years, a 16% reduction in nonvertebral fractures and a 36% reduction in hip fractures in patients with high risk of hip fracture.[15] The medication was well tolerated, and the safety profile was similar to that in younger patients. Although very rare, strontium ranelate can induce DRESS (drug rash with eosinophilia and systemic symptoms). Recently, it has been demonstrated that strontium ranelate reduces radiological progression and pain in patients with knee osteoarthritis. This is important, because osteoporosis and osteoarthritis often coexist in the elderly, and only symptomatic drugs are available in osteoarthritis.[16]

RALOXIFENE

Raloxifene is a selective oestrogen receptor modulator that acts as an oestrogen agonist for bone, lipids and the coagulation system, and as an oestrogen antagonist on breast and uterus. It has a preventive effect on vertebral fractures, but not on hip fractures.[17,18] Additionally it has a protective effect on breast cancer. However, as with oestrogen use, it is associated with an increased risk for venous thrombosis. Raloxifene is not very often prescribed for the prevention of osteoporotic fractures because it has only been proven that it reduces vertebral fractures and because of its side effects. It might be an attractive antiosteoporotic drug in relatively young women (around 60-65 years of age) with oestrogen receptor positive breast cancer.

PTH

Nowadays, two parathyroid hormone (PTH) analogues are available for the treatment of established osteoporosis in postmenopausal women (PTH 1-34 and PTH 1-84).

These PTH analogues are unique anabolic drugs since they not only more or less preserve the BMD by blocking osteoclast activity (such as bisphosphonates), they also build up new bone, by increasing the number of osteoblasts, resulting in an increase in the percent bone-forming surfaces with little effect on bone resorption.[19] Recent data have shown that intermittent PTH analogues interfere with the WnT signalling pathway, by blocking sclerostin, leading to stimulated bone formation.[20]

In the Fracture Prevention Trial (FPT), a multicentre, randomised, double-blind, placebo-controlled trial, 1637 postmenopausal women with an average age of 69 years, an average T-score of -2.6 and at least one prevalent osteoporotic vertebral fracture at the beginning of the study, were included.[21] New vertebral fractures occurred in 14% of the women in the placebo group and in 5% and 4%, respectively, of the women in the 20 μg and 40 μg PTH 1-34 groups; the respective relative risks, as compared with the placebo group, were 0.35 and 0.31 (95% CI intervals 0.22 to 0.55 and 0.19 to 0.50). New nonvertebral fragility fractures occurred in 6% of the women in the placebo group and in 3% of those in each PTH 1-34 group: relative risk 0.47 and 0.46, respectively (95% CI 0.25 to 0.88 and 0.25 to 0.861). No reduction in hip fractures was observed, probably related to the low number of hip fractures in the study (four hip fractures in the whole study).

In the TOP (Treatment of Osteoporosis with Parathyroid Hormone) study with PTH 1-84, a multicentre, randomised, double-blind, placebo-controlled clinical trial on 2532 postmenopausal women either with or without prevalent osteoporotic vertebral fractures, a relative risk reduction of new vertebral fractures was found: 0.42 (95% CI 0.24 to 0.72), but no reduction in nonvertebral and/or hip fractures.[22] The key question is whether PTH 1-84 is less effective than PTH 1-34, or that the design of the study plays an important role, e.g. the enrolment of patients with a lower baseline fracture risk.

Recently, the EFOS (European Forsteo Observation Study) data were published, a large observational study in 1648 patients in eight European countries, all treated for 18 months with teriparatide.[23] In general, these patients had

severe osteoporosis, and several of them had co-morbidities and/or used co-medication that made them not eligible for the above-mentioned phase III trials. The main outcome of the study was a substantial decrease in fracture rate over time: a 47% decrease in fracture rate in the last six-month period compared with the first six-month period. Moreover, a substantial decrease in back pain was found: visual analogue scale at baseline was 57.7 mm, and this was reduced by 25.8 mm after 18 months of treatment ($p<0.001$). In addition to that, an increase in quality of life was observed.

Given the fact that glucocorticoids (GC) induce apoptosis of osteoblasts and osteocytes, with a subsequent inhibiting effect on bone formation, an anabolic drug would, at least theoretically, be preferred to a bisphosphonate for the treatment of glucocorticoid-induced osteoporosis (GIOP).[24] In 2007, PTH 1-34 (20 μg/day) was compared with the active comparator alendronate (10 mg/day) for treating GC-induced osteoporosis in a 36-month, randomised, double-blind, controlled trial in 428 subjects with osteoporosis who had received prednisone 5 mg/day or more for at least three months.[25] A reduction in vertebral fractures in the PTH 1-34 group versus the alendronate group was observed: (3 [1.7%] versus 13 [7.7%]; $p = 0.007$), but no significant difference in the incidence of non-vertebral fractures. In an editorial by Phil Sambrook it was concluded that for patients with low bone mineral density who are receiving long-term GC therapy, teriparatide should be considered as a potential first-line therapy.[26] However, at least partly related to the high cost price, reimbursement of teriparatide (and PTH 1-84) is limited: e.g. in the Netherlands it is only reimbursed for postmenopausal women, and since 1 March 2013 also for men, with two prevalent vertebral fractures who suffer from a third fracture during treatment with bisphosphonates or strontium ranelate.[19]

DENOSUMAB

Denosumab is a really new approach to the prevention of osteoporotic fractures. It is a fully human monoclonal antibody that binds to RANKl and inhibits the RANKl-RANK interaction, resulting in suppressed formation, function and survival of osteoclasts.[27] During treatment with denosumab, bone resorption is strongly inhibited, as shown by a strong reduction in serum C-telopeptide, a marker of bone resorption, one month and six months after subcutaneous injection: -86% and -72%, respectively.[28] In the randomised, pivotal phase III trial, 7868 postmenopausal women with a T-score between -2.5 and -4 were enrolled, and were treated with subcutaneous injections of 60 mg of denosumab or placebo every six months for three years. Remarkably, only 24% of the patients had vertebral fractures at baseline, indicating that fracture risk was relatively low in this patient group. Nevertheless, a striking reduction in the number of patients with new vertebral fractures, the primary endpoint, was found: relative risk 0.32, 95% CI 0.24 to 0.41. In an accompanying editorial is was suggested that a difference was observed between moderate reductions of vertebral fractures for oral bisphosphonates and strontium ranelate, and much larger reductions, for zoledronic acid and denosumab.[29] In addition, a risk reduction of 40% was found for hip fractures and (only) 20% for nonvertebral fractures.

No significant difference was found in serious infections or malignancies; eczema and cellulitis were more frequently reported. As far as we know, no phase IV studies are currently underway in the Netherlands observing the side effects of denosumab in clinical practice in osteoporotic patients with co-morbidity and/or co-medication.

In a follow-up study, patients were eligible to enter a two-year extension study: thus, patients were treated with five years of denosumab, or with two years of denosumab, after three years with placebo.[30] In the five-year denosumab group, BMD increased at the lumbar spine to 13.7%, and to 7.0% at the hips; in the crossover group to 7.7% and 4.0% respectively. Apart from this large increase in BMD, the yearly incidence of both vertebral and nonvertebral fractures were comparable with the relatively low fracture incidence in the denosumab group in the first three years of the study (despite ageing).

In human rheumatoid arthritis (RA) patients, twice-yearly subcutaneous injections of 60 mg and 180 mg of denosumab to RA patients treated with methotrexate not only improved BMD of the lumbar spine and hip but also inhibited structural joint damage.[31] Both dosages prevented progression of erosions, already after six months on MRI and after 12 months on conventional X-rays. In addition, an increased BMD of the hand measured with DXA was observed, while no effect was observed on joint space narrowing. These data indicate that both local and generalised bone loss in RA can be protected by using potent antiresorptive therapies specifically targeting osteoclasts without effecting inflammation.

Cathepsin K inhibitors

The structure and the physiological role of cathepsin K was discovered in 1995; it was found that cathepsin K is the protease that primarily induces the degradation of bone matrix by osteoclasts.[32] Since then, several cathepsin K inhibitors have been developed, while the development was blocked in one of them because of serious side effects (scleroderma-like changes in the skin). For odanacatib, a selective cathepsin K-inhibitor, reliable data are available from phase II studies, and the phase III study is nearly finished. In a randomised controlled trial in 339 patients,

odanacatib 50 mg once weekly was compared with placebo: a greater increase in the BMD of both the lumbar spine and the total hip was observed: 5.5% versus -0.2% and 3.2% versus -0.9%, respectively.[33] Although this increase is impressive, and probably larger than for oral bisphosphonates, it is not yet clear how to extrapolate this to (additional) fracture reduction. During treatment with odanacatib, one very exciting phenomenon occurs: while bone resorption and bone formation are usually coupled, there seems to be some uncoupling in odanacatib-treated patients. For example, serum C-terminal telopeptide (CTX) decreased during treatment with odanacatib, more or less comparable with antiresorptive drugs, while markers of bone formation only initially decrease but then gradually return back to baseline. It is thought that cathepsin K targets the resorption process itself, without an osteoclast-medicated effect on bone formation. Nowadays, we can only speculate whether the absence of uncoupling is not only scientifically and theoretically attractive, but also clinically relevant. A phase III trial with hip fractures as one of the endpoints was terminated in July 2012 because of robust efficacy data; the final results are expected in 2013.

MONOCLONAL ANTIBODIES AGAINST SCLEROSTIN

Sclerosteosis and Van Buchem disease are two closely related rare disorders resulting from endosteal hyperostosis, which are characterised by progressive generalised osteosclerosis, particularly in the mandible and skull, sometimes complicated by entrapment of cranial nerves.[34] Sclerosteosis is caused by a genetic defect on chromosome 17q12-21, encoding for the protein sclerostin; in Van Buchem disease a modification downstream of the same gene was found. In healthy adults, sclerostin is expressed by osteocytes, but not in patients with sclerosteosis and Van Buchem disease sclerostin has an inhibiting effect on bone formation by antagonising the Wnt-signalling pathway. Recently, it has been elucidated that the WnT-signalling pathway plays an important role in bone formation.[34] It is a complex system that can be inhibited by sclerostin, produced by osteocytes, and by Dkk-1. Dkk-1 is upregulated in patients with active RA and in patients treated with glucocorticoids, leading to inhibited bone formation. Theoretically, it is very attractive to develop a strategy to block sclerostin, e.g. by monoclonal antibodies. In a recently published dose-escalating single-dose phase 1 trial it was demonstrated that one single (subcutaneous) injection of a monoclonal antibody against sclerostin markedly increased bone formation markers and BMD: an increase in BMD of 5.3% at the lumbar spine and 2.8% at the total hip was found 85 days after one single injection of 10 mg/kg![35] These data are promising, and the very strong bone formation stimulating effect may be very helpful in patients with severe osteoporosis, although the optimal regimen and dosage should be further investigated.

SUMMARY

Nowadays, the oral bisphosphonates alendronate and risedronate are first choice in the treatment of osteoporosis, because of their effectiveness and tolerability in the majority of patients, while they also have a low cost price. However, the use of bisphosphonates can be associated with side effects: not only the well-known upper gastrointestinal side effects, but also (spontaneous) atypical fractures of the femur and aseptic necrosis of the jaw. The intravenous use of zoledronic acid might be an attractive alternative for those patients who do not tolerate oral bisphosphonates due to gastrointestinal side effects of gastrointestinal contraindications. Strontium ranelate has, next to an antiresorptive effects, also anabolic effects and might particularly be interesting in the elderly, because of the hip fracture reduction in those individuals above 74 years. In addition, it has been demonstrated that strontium ranelate reduces radiological progression and pain in patients with knee osteoarthritis.

Several new drugs are already available or are in the pipeline: these drugs have a completely different mode of action, and seem to induce large changes in BMD. For teriparatide and denosumab substantial decreases in fracture rate have already been documented; both drugs can be prescribed in daily practice. Denosumab is an elegant way of treating osteoporosis since it has the advantage that the favourable effect (vertebral and nonvertebral, including hip fracture reduction) is possible with only two subcutaneous injections per year. Teriparatide is the only drug currently available that has a strong anabolic effect: it leads not only to fracture reduction, but also to reduction in back pain and increased quality of life in elderly postmenopausal women with severe osteoporosis.

For the cathepsin-K antagonist odanacatib fracture data are not (yet) available; for monoclonal antibodies against sclerostin it will probably take some years before phase III trials are finished. Of course, an eventual favourable fracture rate has to be outweighed against data on side effects, cost price of the drugs, and comparisons with already available drugs, such as oral bisphosphonates.

Thus, the number of antiosteoporotic drugs in the field of osteoporosis is rising, and it can be expected that in the coming years very attractive new treatment options can be used in daily practice. Physicians who treat patients with osteoporosis should be aware of the effectiveness,

possible side effects and cost price of these drugs. Apart from that, nonmedical treatment is also still important: adequate calcium and vitamin D supply, regular exercises, prevention of falls, smoking cessation and limiting alcohol intake.

REFERENCES

1. Anonymous. Consensus Development Conference: Prophylaxis and Treatment of Osteoporosis. Am J Med. 1994;646-50.
2. CBO Richtlijn Osteoporose en Fractuurpreventie derde herziening (2011) www.cbo.nl.
3. Lems WF, Raterman HG, van den Bergh JP, et al. Osteopenia: a diagnostic and therapeutic challenge. Curr Osteoporosis Rep. 2011:9:167-72.
4. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best Pract Res Clin Endocrinol Metab. 2011;25:585-91.
5. Gezondheidsraad – Naar een toereikende inname van vitamine D. Gezondheidsraad, 2008; publicatienr. 2008/15.
6. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press; 2011.
7. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;29;341:c3691.
8. Heaney RP, Kopecky S, Maki KC, et al. A review of calcium supplements and cardiovascular disease risk. Adv Nutr. 2012;3:763-71.
9. Black DM, Delmas PD, Eastell R, et al. Once yearly zoledronic acid for treatment of postmenopausal osteoporosis. New Engl J Med. 2007;356:1809-22.
10. Sun K, Liu JM, Sun HX, Lu N, et al. Bisphosphonate treatment and risk of esophageal cancer: a meta-analysis of observational studies. Osteoporos Int. 2012 Oct 6.
11. Khosla S, Bilezikian JP, Dempster DW, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. J Clin Endocrinol Metab. 2012;97:2272-82.
12. .Toissant ND, Elder Kerr PG. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. Clin J Am Soc Nephrol. 2009;4:221-33.
13. Brennan TC, Rybchyn MS, Green W, et al. Osteoblasts play key roles in the mechanisms of action of strontium ranelate. Br J Pharmacol. 2009;157:1291-300.
14. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med. 2004;350:459-68.
15. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab. 2005;90:2816.
16. Reginster JY, Badurski J, Bellamy N, et al. Efficacy and safety of oral strontium ranelate for the treatment of knee osteoarthritis: rationale and design of randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2012, Nov. Epub.
17. Ettinger B, Black DM, Mitlak BH, et al. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA. 1999;282:637-45.
18. Siris ES, Harris ST, Eastell R, et al. Continuing Outcomes Relevant to Evista (CORE) Investigators. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005;20:1514-24.
19. Lems WF, Hamdy NAT, Netelenbos JC. Teriparatide: an anabolic drug for the treatment of patients with osteoporosis. Ned Tijdschr Geneeskd. 2006;150:132-7.
20. Moester MJ, Papapoulos SE, Lowik CW, et al. Sclerostin: current knowledge and future perspectives. Calcif Tissue Int. 2010;87:99-107.
21. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-41.
22. Greenspan SL, Bone HG, Ettinger MP, et al. Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med. 2007;146,326-9.
23. Langdahl BL, Rajzbaum G, Jakob F, et al. Reduction in fracture rate and back pain and quality of life in postmenopausal women treated with teriparatide: 18 month data from the European Forsteo Observational Study (EFOS). Calcif Tissue Int. 2009;85:484-93.
24. Lems WF. Bisphosphonates and glucocorticoids: effects on bone quality. Editorial, Arthritis Rheum. 2007;56:3518-22.
25. Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009;60:3346-55.
26. Sambrook PN. Anabolic therapy in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357:2048-6.
27. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature. 2003;423:337-42.
28. Cummings SR, San Martin J, McClung M, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. New Engl J Med. 2009;361:756-65.
29. Khosla S. Increasing options for the treatment of osteoporosis. New Engl J Med. 2009;361:818-20.
30. Papapoulos S, Chapurlat R. Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Min Res. 2012;694-701.
31. Cohen SB, Dore RK, Lane NE, et al. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in RA. Arthritis Rheum. 2008;58:1299-309.
32. Boonen S, Rosenberg E, Claessens F, et al. Inhibition of cathepsin K for treatment of osteoporosis. Curr Osteoporos Rep. 2012;10:73-9.
33. Bone HG, Mc Clung MR, Roux C, et al. Odanacatib, a cathepsin K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. J Bone Miner Res. 2010;25;937-47.
34. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet. 2011;377:1276-87.
35. Padhi D, Jang G, Stouch B, et al. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. Bone Miner Res. 2011;26:19-26.